General

Guideline Title

Gestational trophoblastic neoplasia.

Bibliographic Source(s)

Alberta Provincial Gynecologic Oncology Team. Gestational trophoblastic neoplasia. Edmonton (Alberta): Alberta Health Services, Cancer Care; 2012 Jun. 9 p. (Clinical practice guideline; no. GYNE-008). [35 references]

Guideline Status

This is the current release of the guideline.

Recommendations

Major Recommendations

Follow-up after evacuation of a molar pregnancy (complete or partial hydatidiform mole) should include (Gerulath et al., 2002):

1. Weekly quantitative human chorionic gonadotropin (hCG) until negative x 3, then monthly x 6 months
2. Regular pelvic examination, at 1, 3, and 6 months post-evacuation
3. Contraception x 6 months (preferably oral contraceptive pill [OCP])
4. Chest x-ray

Indications for Referral to a Gynecologic Oncologist Following Evacuation of a Hydatidiform Mole

Patients who have undergone evacuation of a hydatidiform mole *and* who present with any of the following should be referred to a gynecologic oncologist (Gerulath et al., 2002; Berkowitz & Goldstein, 1996):

- An abnormal β-hCG regression pattern (a 10% or greater rise in β-hCG levels over three weeks or a plateauing β-hCG of three stable values over four weeks)
- A rise in β-hCG following a normal regression pattern
- A histologic diagnosis of choriocarcinoma, placental site trophoblastic tumour, or epithelioid trophoblastic tumour
- High β-hCG levels (greater than 20,000 mIU/mL more than four weeks post-evacuation)
- Persistently elevated β-hCG levels 6 months post-evacuation
- The presence of metastases in addition to abnormal β-hCG levels

Work-up for Gestational Trophoblastic Neoplasia

History and physical exam should be performed, along with the following investigations:

- Blood work: serum β-hCG, complete blood count (CBC) with differential, platelet determinations, clotting function tests, liver function tests, and renal function tests
- Imaging to check for metastases: chest x-ray with computed tomography (CT) scan of the chest if the chest x-ray is negative, CT scans of the abdomen and pelvis, and CT scan or magnetic resonance imaging (MRI) of the brain

Staging and Prognostic Scoring for Gestational Trophoblastic Neoplasia (GTN)

Staging of GTN is based on the Fédération Internationale de Gynecologie et d'Obstétrique (FIGO) system (2009) (Kohorn, 2001):

- Stage I: Disease confined to the uterus
- Stage II: GTN extends outside of the uterus, but is limited to the genital structures (i.e., adnexa, vagina, broad ligament)
- Stage III: GTN extends to the lungs, with or without known genital tract involvement
- Stage IV: All other metastatic sites

Risk assessment is based on several indicators, including age, antecedent pregnancy, interval months from index pregnancy, pretreatment serum β-hCG, largest tumor size (including uterus), site of metastases, number of metastases, and previous failed chemotherapy (see table below) (Kohorn, 2001).

Table. Prognostic Scoring for Gestational Trophoblastic Neoplasia (FIGO, 2009; modified from WHO)

Scores	**0**	**1**	**2**	**4**
Age	<40	≥40	—	—
Antecedent pregnancy	Mole	Abortion	Term	—
Interval months from index pregnancy	<4	4–6	7–12	>12
Pretreatment serum β-hCG (iu/1)	<103	103–104	104–105	>105
Largest tumor size (including uterus)	<3	3–4 cm	≥5 cm	—
Site of metastases	Lung	Spleen, kidney	Gastrointestinal	Liver, brain
Number of metastases	—	1–4	5–8	>8
Previous failed chemotherapy	—	—	Single drug	≥2 drugs

- Low-risk: individuals with a score ≤6 (National Cancer Institute, 2011; American College of Obstetricians and Gynecologists [ACOG], 2008; Kohorn, 2001).
- High-risk: individuals with a score ≥7 (National Cancer Institute, 2011; ACOG, 2008; Kohorn, 2001).

Treatment of Gestational Trophoblastic Neoplasia

Options for the management of GTN are dependent on prognostic scoring and include the following:

Non-metastatic (Stage I) and Low-risk Metastatic (Stages II and III, FIGO score ≤6)

Preferred regimens include:

- Actinomycin-D and methotrexate with folinic acid, given every 2 weeks for 1 to 3 cycles beyond negative β-hCG
  - Actinomycin-D (0.5 mg/m^2 intravenous [IV]) given days 1-2
  - Methotrexate (100 mg/m^2 IV push + 300 mg/m^2 IV) on day 1
  - Folinic acid (15 mg orally [PO], every [q] 6 h x 9 doses starting 24 hours after methotrexate bolus)
- Actinomycin-D (1.25 mg/m^2 IV), given every 2 weeks for 1 to 3 cycles beyond negative β-hCG
- Methotrexate (30 mg/m^2 or 50 mg/m^2 intramuscular [IM]), given weekly for 1 to 3 cycles beyond negative β-hCG

Other regimens include:

- Methotrexate (50 mg/m^2 IM, days 1, 3, 5, 7) and folinic acid (7.5 mg oral, days 2, 4, 6, 8), given every 2 weeks for 1 to 3 cycles beyond negative β-hCG
- Methotrexate (100 mg/m^2 IV) and folinic acid (15 mg oral, q 6 h x 4 doses starting 24 h after methotrexate), given weekly for 1 to 3 cycles

beyond negative β-hCG

In select patients, consider performing adjuvant surgery (i.e., hysterectomy).

High-risk Metastatic (Stages II and III, FIGO score ≥7 and Stage IV)

Preferred regimens include:

- EMA/CO multi agent chemotherapy, given every 2 weeks for 3 cycles beyond negative β-hCG
  - Etoposide (100 mg/m^2 IV, days 1, 2)
  - Actinomycin-D (0.5 mg IV push days 1, 2)
  - Methotrexate (300 mg/m^2 IV, day 1)
  - Folinic acid (15 mg PO, q 12 h, days 2, 3)
  - Vincristine (0.8–1.0 mg/m^2 IV, day 8)
  - Cyclophosphamide (600 mg/m^2 IV, day 8)
- EMA/CE multi agent chemotherapy, given every 2 weeks for 3 cycles beyond negative β-hCG
  - Course 1: same as EMA/CO
  - Course 2: etoposide (100 mg/m^2 IV, day 8), cisplatin (80 mg/m^2 IV, day 8), plus magnesium supplementation (30 ml PO, q 12 h, day 1)
- MACE multi agent chemotherapy
  - Cisplatin (30 mg/m^2 IV, days 1-3)
  - Etoposide (50 mg PO, days 1-10)
  - Actinomycin-D (0.5 mg/m^2 IV, days 8 and 9)
  - Methotrexate (100 mg/m^2 bolus + 300 mg/m^2 IV, day 8)
  - Folinic acid (15 mg PO, q 6 h x 9 doses starting 24 hours after methotrexate bolus)

Other regimens include:

- BEP multi agent chemotherapy
  - Bleomycin: 30 units per week
  - Etoposide: 100 mg/m^2, days 1-5
  - Cisplatin: 20 mg/m^2, days 1-5
- 5-FU/actinomycin-D multi agent chemotherapy (as second-line therapy), given every 2 weeks for 4-7 cycles beyond negative β-hCG
  - 5-FU: 1500 mg/m^2 IV, days 1-5
  - Actinomycin-D: 0.5 mg/m^2 IV push
- Adjuvant surgery for resection of metastases in selected patients
- Radiotherapy in selected patients

Follow Up for Gestational Trophoblastic Neoplasia

Serial serum β-hCG measurements should be determined as follows:

- Every 1-2 weeks for the first 3 months or while elevated
- Then q 1-2 months for a total follow-up of one year

Patients should be advised about future pregnancy:

- Pregnancy should be avoided until β-hCG levels have been normal for a minimum of 6 months up to one year (depending on risk score) following chemotherapy for gestational trophoblastic neoplasia; however, among patients who do conceive within 6-12 months of treatment, a favorable outcome is likely.
- The combined OCP is safe for use by women with GTN.
- First trimester ultrasound and serum β-hCG testing is recommended for women who become pregnant for the first time after treatment for GTN. In addition, β-hCG testing at 6-8 weeks after delivery may be performed.

In patients for whom hormone replacement therapy (HRT) is indicated, HRT may be used safely once β-hCG levels have returned to normal.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Gestational trophoblastic neoplasia (GTN):

- Non-invasive and invasive mole
- Choriocarcinoma
- Placental site trophoblastic tumour
- Epithelioid trophoblastic tumour

Guideline Category

Counseling

Diagnosis

Evaluation

Management

Risk Assessment

Treatment

Clinical Specialty

Family Practice

Internal Medicine

Obstetrics and Gynecology

Oncology

Pathology

Radiation Oncology

Radiology

Surgery

Intended Users

Advanced Practice Nurses

Nurses

Physician Assistants

Physicians

Guideline Objective(s)

To recommend options for the management of gestational trophoblastic neoplasia (GTN), based on the best evidence available

Target Population

Women with gestational trophoblastic neoplasia, including invasive mole, choriocarcinoma, and placental site trophoblastic tumour

Interventions and Practices Considered

1. Follow-up after evacuation of a molar pregnancy
    - Weekly quantitative human chorionic gonadotropin (hCG) for 3 weeks, then monthly for 6 months
    - Regular pelvic examination, at 1, 3, and 6 months post-evacuation
    - Contraception for 6 months (preferably oral contraceptive pill [OCP])
    - Chest x-ray
2. Referral to gynecological oncologist as indicated by hCG levels, histological diagnosis, or presence of metastases
3. Work-up for gestational trophoblastic neoplasia (GTN)
    - History and physical exam
    - Blood work: serum β-hCG, complete blood count (CBC) with differential, platelet determinations, clotting function tests, liver function tests, and renal function tests
    - Imaging for metastases: chest x-ray, computed tomography (CT) scan of the chest, CT scans of the abdomen and pelvis, and CT scan or magnetic resonance imaging (MRI) of the brain
4. Staging and prognostic scoring of GTN based on the Fédération Internationale de Gynecologie et d'Obstétrique (FIGO) system
5. Treatment based on prognostic scoring
    - Chemotherapy
    - Adjuvant surgery
    - Radiotherapy
6. Follow-up
    - Serial serum β-hCG measurements
    - Advice to avoid pregnancy until β-hCG levels have been normal for a minimum of 6 months following chemotherapy
    - Use of combined OCP
    - First trimester ultrasound and serum β-hCG testing for women who become pregnant

Major Outcomes Considered

- Effectiveness of laboratory and imaging tests
- Complete response rates
- Hematologic toxicities
- Cure rates
- Overall survival
- Remission rates
- Risk of subsequent abnormal pregnancy

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Research Questions

Specific research questions to be addressed by the guideline document were formulated by the guideline lead(s) and Knowledge Management (KM) Specialist using the PICO question format (patient or population, intervention, comparisons, outcomes).

Guideline Questions

- Which patients should be referred to a gynecologic oncologist after evacuation of a hydatidiform mole?
- What investigations are appropriate for the work-up of gestational trophoblastic neoplasia (GTN)?
- How should GTN be staged and scored prognostically?
- How should GTN be managed?
- What investigations are recommended for the follow-up of patients with GTN?

Search Strategy

The Ovid Medline, PubMed, EMBASE, and Cochrane databases were searched for relevant articles published between 1965 and 2011 October. Clinical practice guideline databases (e.g., National Guideline Clearinghouse, CancerView, etc.) were also searched for evidence relevant to the topic, published between 2006 and 2011 October.

For the evidence on work-up, search terms included: gestational trophoblastic neoplasia AND workup or chest x-ray or magnetic resonance imaging or computed tomography or pelvic ultrasound or complete blood count or beta hCG or liver function tests or renal function tests or marrow function tests. A total of 1,086 citations were returned; only studies that looked at blood work or imaging tests in a cohort of patients (i.e., ten or more) with diagnosed gestational trophoblastic neoplasia (no case studies) and were published in English from 2000 to 2011 October were included. The terms gestational trophoblastic neoplasia AND metastases were also searched, with the results limited to clinical trials only. In total, nine articles and four guidelines were included as evidence. For the evidence on staging and prognostic scoring, as well as evidence on follow-up, the term gestational trophoblastic neoplasia was searched using the National Guideline Clearinghouse database as well as individually searching Canadian cancer guidelines developers' websites. For the evidence on management, the terms gestational trophoblastic neoplasia and chemotherapy were searched in the EMBASE, Ovid Medline and PubMed databases, with results limited to clinical trials published from 2000 to 2011 October that looked at a single agent or multi-agent regimen in a cohort of patients (i.e., ten or more) with diagnosed gestational trophoblastic neoplasia.

Existing guidelines considered for the review included those published by the following groups: Society of Obstetricians and Gynaecologists of Canada (2002), National Cancer Institute (2011), American College of Obstetricians and Gynecologists (2008), and BC Cancer Agency (2000).

Number of Source Documents

Not stated

Methods Used to Assess the Quality and Strength of the Evidence

Not stated

Rating Scheme for the Strength of the Evidence

Not applicable

Methods Used to Analyze the Evidence

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Evidence was selected and reviewed by a working group comprised of members from the Alberta Provincial Gynecologic Oncology Tumour Team and a Knowledge Management (KM) Specialist from the Guideline Utilization Resource Unit (GURU). A detailed description of the

methodology followed during the guideline development process can be found in the Guideline Utilization Resource Unit Handbook (see the "Availability of Companion Documents" field).

Evidence Tables

Evidence tables containing the first author, year of publication, patient group/stage of disease, methodology, and main outcomes of interest are assembled using the studies identified in the literature search. Existing guidelines on the topic are assessed by the KM Specialist using portions of the AGREE II instrument (http://www.agreetrust.org/) and those meeting the minimum requirements are included in the evidence document. Due to limited resources, GURU does not regularly employ the use of multiple reviewers to rank the level of evidence; rather, the methodology portion of the evidence table contains the pertinent information required for the reader to judge for himself the quality of the studies.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Formulating Recommendations

The working group members formulate the guideline recommendations based on the evidence synthesized by the Knowledge Management (KM) Specialist during the planning process, blended with expert clinical interpretation of the evidence. As detailed in the Guideline Utilization Resource Unit Handbook (see the "Availability of Companion Documents" field), the working group members may decide to adopt the recommendations of another institution without any revisions, adapt the recommendations of another institution or institutions to better reflect local practices, or develop their own set of recommendations by adapting some, but not all, recommendations from different guidelines.

The degree to which a recommendation is based on expert opinion of the working group and/or the Provincial Tumour Team members is explicitly stated in the guideline recommendations. Similar to the American Society of Clinical Oncology (ASCO) methodology for formulating guideline recommendations, the Guideline Utilization Resource Unit (GURU) does not use formal rating schemes for describing the strength of the recommendations, but rather describes, in conventional and explicit language, the type and quality of the research and existing guidelines that were taken into consideration when formulating the recommendations.

An effort was made to either adapt or adopt the most appropriate guidelines from other sources so that work wasn't duplicated. An evidence based perspective was used to draft proposals. Where evidence was weak, recommendations were based on group consensus.

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

Internal Peer Review

Description of Method of Guideline Validation

This guideline was reviewed and endorsed by the Alberta Provincial Gynecologic Oncology Tumour Team.

When the draft guideline document is completed, revised, and reviewed by the Knowledge Management Specialist and the working group members, it is sent to all members of the Provincial Tumour Team for review and comment. The working group members then make final revisions

to the document based on the received feedback, as appropriate. Once the guideline is finalized, it is officially endorsed by the Provincial Tumour Team Lead and the Executive Director of Provincial Tumour Programs.

Evidence Supporting the Recommendations

References Supporting the Recommendations

American College of Obstetricians and Gynecologists (ACOG). Diagnosis and treatment of gestational trophoblastic disease. Washington (DC): American College of Obstetricians and Gynecologists (ACOG); 2004 Jun. 13 p. (ACOG practice bulletin; no. 53). [49 references]

Berkowitz RS, Goldstein DP. Chorionic tumors. N Engl J Med. 1996 Dec 5;335(23):1740-8. [100 references] PubMed

Gerulath AH, Ehlen TG, Bessette P, Jolicoeur L, Savoie R, Society of Obstetricians and Gynaecologists of Canada, Gynaecologic Oncologists of Canada, Society of Canadian Colposcopists. Gestational trophoblastic disease. J Obstet Gynaecol Can. 2002 May;24(5):434-46. PubMed

Kohorn EI. The new FIGO 2000 staging and risk factor scoring system for gestational trophoblastic disease: description and critical assessment. Int J Gynecol Cancer. 2001 Jan-Feb;11(1):73-7. PubMed

National Cancer Institute (NCI). Cancer topics: gestational trophoblastic tumors and neoplasia treatment. Bethesda (MD): National Cancer Institute (NCI); 2011 Aug.

Type of Evidence Supporting the Recommendations

The type of evidence supporting the recommendations is not specifically stated.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate management of gestational trophoblastic neoplasia (GTN)

Potential Harms

Hematologic toxicities and myelosuppression associated with chemotherapy regimens

Contraindications

Contraindications

Pregnancy should be avoided until β-human chorionic gonadotropin (hCG) levels have been normal for a minimum of 6 months up to one year (depending on risk score) following chemotherapy for gestational trophoblastic neoplasia.

Qualifying Statements

Qualifying Statements

The recommendations contained in this guideline are a consensus of the Alberta Provincial Gynecologic Oncology Team and are a synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.

Implementation of the Guideline

Description of Implementation Strategy

- Present the guideline at the local and provincial tumour team meetings and weekly rounds.
- Post the guideline on the Alberta Health Services (AHS) website.
- Send an electronic notification of the new guideline to all members of AHS, Cancer Care.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

Alberta Provincial Gynecologic Oncology Team. Gestational trophoblastic neoplasia. Edmonton (Alberta): Alberta Health Services, Cancer Care; 2012 Jun. 9 p. (Clinical practice guideline; no. GYNE-008). [35 references]

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2012 Jun

Guideline Developer(s)

CancerControl Alberta - State/Local Government Agency [Non-U.S.]

Source(s) of Funding

Alberta Health Services, Cancer Care

Guideline Committee

Alberta Provincial Gynecologic Oncology Tumour Team

Composition of Group That Authored the Guideline

Not stated

Financial Disclosures/Conflicts of Interest

Participation of members of the Alberta Provincial Gynecologic Oncology Team in the development of this guideline has been voluntary and the authors have not been remunerated for their contributions. There was no direct industry involvement in the development or dissemination of this guideline. Alberta Health Services – Cancer Care recognizes that although industry support of research, education and other areas is necessary in order to advance patient care, such support may lead to potential conflicts of interest. Some members of the Alberta Provincial Gynecologic Oncology Team are involved in research funded by industry or have other such potential conflicts of interest. However the developers of this guideline are satisfied it was developed in an unbiased manner.

Guideline Status

This is the current release of the guideline.

Guideline Availability

Electronic copies: Available in Portable Document Format (PDF) from the Alberta Health Services Web site .

Availability of Companion Documents

The following is available:

- Guideline utilization resource unit handbook. Edmonton (Alberta): Alberta Health Services, Cancer Care; 2011 Dec. 5 p. Electronic copies: Available in Portable Document Format (PDF) from the Alberta Health Services Web site .

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on December 6, 2012. The information was verified by the guideline developer on January 14, 2013.

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